REMARKS

Applicants have amended claim 6 to recite "a 4'- $(CH_2)_n$-O-2' bridge, wherein n is 1 or 2." Support for this amendment can be found throughout the specification as filed, for example, at page 16, lines 13-15. For the reasons stated below, Applicants respectfully traverse the rejections of the pending claims.

35 U.S.C. § 102(e) – Anticipation

The Examiner rejects claims 1, 2, 11, and 13 under 35 U.S.C. § 102(e) as anticipated by Diamond et al. (WO 02/72130). The Examiner asserts that Diamond discloses a composition comprising an antisense oligonucleotide "which oligonucleotide is 100% complementary to SEQ ID NO. 17 (see Accession No. ABV73748, and example 1, page 16 of Diamond et al; see accompanying alignment data between Acc. No. ABV73748 and the instantly claimed SEQ ID NO. 64). Applicants respectfully traverse.

According to the text and table on page 16 of Diamond, Diamond discloses two PCR primers to human Bax: one sense primer and one antisense primer. Based on the sequence of the sense primer and the statement on page 1 of the alignment accompanying the Office Action, the sequence relied on by the Examiner is the sense PCR primer for Bax. The alignment provided by the Examiner is apparently an alignment between the reverse complement of the sense primer sequence in Diamond and SEQ ID NO: 64 of the present invention. Therefore, the sense primer sequence disclosed in Diabmond is not 100% complementary to SEQ ID NO: 17, but rather has some level of identity to SEQ ID NO: 17. On the other hand, the antisense PCR primer disclosed in the table on page 16 of Diamond apparently does not have any identity with SEQ ID NO: 64 of the present invention. As such, neither of the PCR primers disclosed on page 16 of Diamond expressly or inherently disclose each and every limitation of the pending claims, and therefore Diamond does not anticipate the rejected claims. For at least this reason, Applicants request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 11 and 13 under 35 U.S.C. § 102(e) over Diamond.

35 U.S.C. §103(a) – Obviousness

The Examiner rejects claims 1-9 and 11-19 under 35 U.S.C. § 103(a) as unpatentable over Diamond et al. (WO 02/72130) as applied in the 35 U.S.C. § 102(e) rejection above, in view of Korsmeyer, Milner *et al.* and McKay *et al.* The Examiner relies on Diamond as discussed above in the 102(e) rejection, but states that Diamond does not disclose various features of the claims such as specific chemistries. The Examiner relies on the secondary references to supply the subject matter missing from Diamond. *Office Action* at 4-6. The Examiner argues that it would have been obvious to design and utilize antisense "comprising at least 12 contiguous nucleobases of SEQ ID NO: 64 to inhibit the expression of SEQ ID NO: 17…because Diamond teaches this antisense sequence." *Office Action* at 6 (emphasis added). The Examiner also asserts that based on the methods of designing and testing oligonucleotides disclosed in Milner and McKay, one of skill in the art would successfully "identify numerous antisense oligonucleotides…including the well known region targeted by SEQ ID NO: 64." *Office Action* at 7 (emphasis added).

Applicants respectfully traverse because the Examiner has failed to demonstrate that the cited references teach or suggest each and every element of the claimed compounds, compositions and methods as required to establish a *prima facie* case of obviousness. The pending claims recite in part an oligonucleotide "having a nucleobase sequence comprising an at least 8 consecutive nucleobase portion of SEQ ID NO: 64."

As discussed above, the sequence disclosed in Diamond which is relied on by the Examiner is a sense primer for PCR amplification. The alignment provided by the Examiner is apparently an alignment between the reverse complement of the sequence of the sense primer in Diamond and SEQ ID NO: 64 of the present invention. Furthermore, the antisense PCR primer disclosed in Diamond apparently does not have any identity with SEQ ID NO: 64. Therefore, contrary to the Examiner's assertion, Diamond does not teach an antisense oligonucleotide comprising "at least 12 contiguous nucleobases of SEQ ID NO: 64," and the region targeted by SEQ ID NO: 64 is not a "well known" target region for antisense.

Applicants submit that the Examiner is relying on unsupported hindsight reasoning to reject the pending claims. The Examiner provides no evidence or reasoning to support the conclusion that it would be obvious to design an oligonucleotide comprising at least 8

nucleotides of SEQ ID NO: 64 – there is no support for the assertion that one of skill in the art would design an antisense molecule based on the sense primer for a PCR reaction.

In addition, even if one assumes for the sake of argument that one of skill in the art "would have been motivated to utilize [the method of Milner] of finding optimal antisense oligonucleotides" to the target gene (*Office Action* at 6), the Examiner has failed to establish how or why one would arrive at "the well known region targeted by SEQ ID NO: 64" (*id.* at 7) if one of skill in the art applied the cited references to the target gene. The Examiner offers no support for this assertion, and as noted above, Diamond does not disclose targeting the region of SEQ ID NO: 64 with antisense – it is not a "well known" target region. Nor is there any basis in the cited references to believe that a compound comprising a portion of SEQ ID NO: 64 would be an active antisense molecule, since the Examiner has not shown any relationship between antisense compounds and sense PCR primers.

The only basis the Examiner has for concluding that a compound comprising at least 8 nucleotides of SEQ ID NO: 64 is a desirable compound for inhibition of the target gene is Applicants' disclosure of SEQ ID NO: 64. This is nothing more than impermissible hindsight.

Applicants submit that the Examiner's unsupported assertions are not common knowledge or well-known, and therefore represent official notice without documentary evidence. Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). The cited references do not provide the required evidence, as the Examiner has not shown that any of the references disclose or suggest a compound comprising at least 8 nucleotides of SEQ ID NO: 64.

Given that the Examiner's assertion that Diamond discloses an antisense compound comprising an 8 base portion of SEQ ID NO: 64 is erroneous, and the Examiner has failed to explain how or why one would arrive at that sequence independent of Applicants' disclosure, the Examiner has failed to establish a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request that the Examiner withdraw the rejection of the pending claims under 35 U.S.C. § 103(a) over Diamond in view of Korsmeyer, Milner *et al.* and McKay *et al.*

Unexpected Results Must Be Considered

Finally, even if the Examiner has established a *prima facie* case of obviousness, a point which Applicants do not concede, Applicants submit that compounds and methods of the currently pending claims have unexpected properties which are more than sufficient to overcome any *prima facie* case of obviousness that the Examiner has presented. "The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that 'evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.'" *M.P.E.P. §716.01(a)* (emphasis added). Applicants respectfully request consideration of the following evidence.

In particular, Applicants note that SEQ ID NO: 64 exhibits 84% inhibition of the target as reported in Table 1 of the specification. This is clearly unexpected, as none of the cited references even disclose SEQ ID NO: 64, or provide any reason for one of skill in the art to expect that SEQ ID NO: 64 would demonstrate such a high level of inhibition. For this additional reason, Applicants request that the Examiner withdraw the rejection of the pending claims under 35 U.S.C. § 103(a) as obvious over the cited references.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patent(s) or application(s). Applicants encourage the Examiner to review and monitor the prosecution of the following patent(s) and/or application(s) throughout the pendency of this application.

Patent/Serial No.	Title	Issued/Filed
09/908,147	Antisense modulation of BCL2-associated X protein expression	07-17-2001

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/14/09

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